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NO compound
solvent
propellant
only.

(54) Title: MEDICINAL AEROSOL FORMULATIONS

(57) Abstract

A solution aerosol formulation containing a drug, a glycerol phosphatide, and a propellant system containing n-butane, dimethylether, or a mixture thereof.

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MEDICINAL AEROSOL FORMULATIONS5 BACKGROUND OF THE INVENTIONField of the Invention

This invention relates to medicinal aerosol formulations and in particular to formulations suitable for pulmonary, nasal, buccal, or topical administration
10 which are at least substantially free of chlorofluorocarbons.

Description of the Related Art

Since the metered dose pressurized inhaler was
15 introduced in the mid 1950's, inhalation has become the most widely used route for delivering bronchodilator drugs and steroids to the airways of asthmatic patients. Compared with oral administration of bronchodilators, inhalation offers a rapid onset of
20 action and a low instance of systemic side effects. More recently, inhalation from a pressurized inhaler has been a route selected for the administration of other drugs, e.g., ergotamine, which are not primarily concerned with treatment of a bronchial malady.

25 The metered dose inhaler is dependent upon the propulsive force of a propellant system used in its manufacture. The propellant generally comprises a mixture of liquified chlorofluorocarbons (CFC's) which are selected to provide the desired vapor pressure and
30 stability of the formulation. Propellants 11, 12 and 114 are the most widely used propellants in aerosol formulations for inhalation administration.

The aerosol formulations are generally in the form of a suspension of drug in the propellant utilizing a
35 surfactant. There are few drugs which are soluble in aerosol propellants and solution formulations have been prepared using a polar cosolvent, such as ethanol.

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European Patent No. 209547 discloses solution formulations of drugs in chlorofluorocarbon propellants in the presence of a glycerol phosphatide.

In recent years it has been established that CFC's
5 react with the ozone layer around the earth and contribute towards its depletion. There has been considerable pressure around the world to reduce substantially the use of CFC's, and various Governments have banned the "non-essential" use of CFC's. Such
10 "non-essential" uses include the use of CFC's as refrigerants and blowing agents, but heretofore the use of CFC's in medicines, which contributes to less than 1% of the total use of CFC's, has not been restricted. Nevertheless, in view of the adverse effect of CFC's on
15 the ozone layer it is desirable to seek alternative propellant systems which are suitable for use in inhalation aerosols.

Various alternative propellants have been suggested for use in place of CFC's. European Patent
20 Application No. 89312270.5 discloses that 1,1,1,2-tetrafluoroethane (Propellant 134a), may be employed as a propellant for aerosol formulations suitable for inhalation therapy when used in combination with a compound (hereinafter an "adjuvant") having a higher
25 polarity than Propellant 134a. The adjuvant should be miscible with Propellant 134a in the amounts employed. Suitable adjuvants include alcohols such as ethyl alcohol, isopropyl alcohol, propylene glycol, hydrocarbons such as propane, butane, isobutane,
30 pentane, isopentane, neopentane, and other propellants such as those commonly referred to as Propellants 11, 12, 114, 113, 142b, 152a 124, and dimethyl ether. Preferred adjuvants are liquids or gases at room temperature (22°C) at atmospheric pressure. The
35 combination of one or more of such adjuvants with Propellant 134a provides a propellant system which has comparable properties to those of propellant systems

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based on CFC's, allowing use of known surfactants and additives in the pharmaceutical formulations. This is particularly advantageous since the toxicity and use of such compounds in metered dose inhalers for drug
5 delivery to the human lung is well established.

It has been suggested that hydrocarbons, such as n-butane, isobutane, and propane be considered as CFC replacements in aerosol formulations. However, it has been found that such hydrocarbons have low densities
10 relative to the drugs in the formulations and that suspension formulations sediment rapidly and are unacceptable. Furthermore, the solubility of many drugs in these hydrocarbons is not sufficient, and solution formulations therefore do not contain suitable
15 amounts of drug.

Summary of the Invention

It has now been found that the solubility of many drugs in certain hydrocarbons and dimethyl ether may be
20 enhanced in the presence of glycerol phosphatide.

Therefore according to the present invention there is provided an aerosol formulation which contains no dispersed phase, comprising: an aerosol propellant system comprising a propellant selected from n-butane,
25 dimethylether, and mixtures thereof; a glycerol phosphatide; and a drug, in which the drug is dissolved in the composition in an amount greater than could be achieved in the absence of glycerol phosphatide.

30 Detailed Description of the Invention

The glycerol phosphatide may be any one of the following compounds; phosphatidylcholine (lecithin), phosphatidylethanolamine (cephalin), phosphatidyl-
35 inositol, phosphatidylserine, diphosphatidylglycerol, or phosphatidic acid.

It has been found that drugs having at least very slight solubility in hydrocarbon propellants will

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exhibit an enhanced solubility in the propellant in the presence of glycerol phosphatide. Surprisingly it has been found that glycerol phosphatides cause complete dissolution of certain drugs in n-butane and dimethylether. It is postulated that this enhanced solubility is attributable to drug in true solution becoming associated with reverse micelles of the glycerol phosphatide which allows further drug to dissolve in the propellant. Thus, the solubilization process is believed to be as follows:

15	drug ----- drug in solution ----- drug associated in propellant with reverse micelles of glycerol phosphatide
----	---

20	"Initial ----- solubilization"	"Micellar solubilization"
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While the compositions of the invention appear visibly to be true solutions since there is no dispersed phase apparent, they are more correctly referred to as micellar solutions.

25 The formulations of the invention can be prepared
by forming a concentrate of glycerol phosphatide with a
drug and propellant. The concentrate can be formed by
simple admixture with agitation and optionally under
heating, e.g., 50°C, until complete dissolution of the
30 drug has been attained. The concentrate can then be
mixed with the remainder of the propellant formulation.

Phosphatidylcholine is the most suitable glycerol phosphatide to use in view of its low toxicity and high drug solubilizing efficacy. Commercial grades of
35 lecithin vary widely in phosphatidylcholine content. Purified phosphatidylcholine (e.g., having phosphatidylcholine content in excess of about 90% by

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weight) is preferred for use in this invention. Phosphatidylcholine purified from soya bean lecithin is readily available commercially and suitable grades include Epikuron™ 200 (Lucas-Meyer) and Lipoid™ S100
5 (Lipoid KG). Both products have a phosphatidylcholine content in excess of 95%.

It has been found that certain drugs which are practically insoluble in hydrocarbon propellants alone can be solubilized by adding a small amount, e.g., up
10 to 5% by weight of a cosolvent, such as ethanol, to the formulation. It is postulated that the cosolvent enhances the initial solubilization step of the solubilization process. Certain commercially available forms of lecithin, e.g., Lipoid™ S45, contain ethanol
15 in addition to their phosphatidylcholine content. With lecithins of this type, the ethanol may likewise enhance drug solubilization in a formulation of the invention.

Suitable drugs for use in the invention include
20 those which exhibit at least a very slight solubility in the propellant system. In general, the drug will be in a relatively non-polar form, e.g., the form of an ester, base, or free alcohol. Highly polar ionic salts of drugs are generally less suitable since it is
25 difficult to solubilize the drug in sufficient quantity even with the presence of a small amount of cosolvent.

The drug is generally present in the formulation in an amount in the range from 0.1 to 15 mg/mL, usually from 2 to 10 mg/mL based on the total volume of the
30 formulation. Suitable medicaments include those disclosed in European Patent Application No. 89312270.5 and include, but are not limited to, albuterol, beclomethasone dipropionate, fentanyl citrate, isoprenaline, rimiterol, pirbuterol, adrenaline,
35 disodium cromoglycate (DSCG), histamine acid sulphate, morphine and its salts, ergotamine, atropine, captopril, propranolol, diazepam, glycerol trinitrate,

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isosorbide dinitrate, isosorbide mononitrate, and ipratropium bromide.

The propellant system contains one or both of n-butane and dimethylether and can include copropellants
5 such as isobutane and propane. The propellant system may include minor amounts of other propellants, but preferably contains no more than 5% by weight of CFCs. More preferably the propellant system is free from CFCs.

10 In general, the compositions comprising drug, glycerol phosphatide, and propellant system contain one to 500, preferably one to 30, more preferably 2 to 10, parts by weight drug based on 100 parts by weight glycerol phosphatide, and 0.01 to 20, preferably 0.01
15 to 10, more preferably 0.01 to 3, parts by weight glycerol phosphatide based on 100 parts by weight propellant system.

The invention will now be illustrated by the following Examples.

20

EXAMPLE 1

	<u>mg/mL</u>
Albuterol	2.00
Lipoid™ S100 phosphatidylcholine	14.00
25 n-butane	563.00
	<hr/>
	579.00

A concentrate was prepared by combining the drug,
30 the phosphatidylcholine, and a portion of the n-butane in a pressure resistant vessel. Dissolution of this concentrate was achieved by heating for 1 hour in a water bath maintained at 55°C.

The solution was then cooled and the remainder of
35 the n-butane was added. The resulting formulation was in the form of a stable solution.

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EXAMPLE 2

		<u>mg/mL</u>
	Albuterol	2.00
	Lipoid™ S100 phosphatidylcholine	14.00
5	n-Butane	125.56
	Dimethylether	502.24
		<hr/>
		643.80

10 The drug, phosphatidylcholine, and n-butane were mixed in a pressure resistant vessel to form a concentrate. Dissolution was achieved by heating for 1 hour in a water bath maintained at 55°C.

15 The solution was then cooled and the dimethylether was added. The resulting formulation was in the form of a stable solution.

EXAMPLE 3

		<u>mg/mL</u>
20	Albuterol	2.00
	Lipoid™ S100 phosphatidylcholine	14.00
	n-Butane	113.32
	Iso-butane	339.96
	Dimethylether	113.32
25		<hr/>
		582.60

30 The formulation was prepared according to the general method of Example 2 and complete dissolution was achieved.

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EXAMPLE 4

		<u>mg/mL</u>
	Beclomethasone Dipropionate	1.00
	Lipoid™ S100 phosphatidylcholine	7.00
5	n-Butane	114.92
	Drivosol™ 32*	344.76
	Dimethylether	114.92
		<hr/>
		582.60
10	*A mixture containing 77 percent isobutane, 4 percent n-butane, and 19 percent propane by weight.	

The drug, phosphatidylcholine, and a portion of
15 the dimethylether were mixed in a pressure resistant vessel to form a concentrate. Dissolution was achieved by agitation at room temperature.

The solution was then cooled to -40°C followed by
addition of the other components of the propellant
20 system. The resulting formulation was in the form of a stable solution.

EXAMPLE 5

		<u>(g)</u>
25	Albuterol	0.007
	Phosphatidylinositol ammonium salt	0.050
	n-Butane	0.400
	n-Butane overage	0.300
30		<hr/>
		0.757

The components were introduced into a
polyethyleneterephthalate vial (15 mL) and a non-
35 metering valve was crimped in place. An n-butane overage of 0.300 g was present in the formulation to allow for evaporation in the head space in the vial.

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A solution was obtained after three hours immersion in a 55°C water bath. The formulation was allowed to stand and cool to room temperature. No precipitation or crystallization was observed.

5

EXAMPLE 6

	<u>(g)</u>
Albuterol	0.014
3-Sn-Phosphatidyl-L-Serine	0.100
10 n-Butane	0.700
n-Butane overage	0.300
	<hr/>
	1.114

15 The formulation was prepared as in Example 5. After immersion in the waterbath for 2 hours a solution was obtained. The formulation was allowed to stand and cool to room temperature. No precipitation or crystallization was observed.

20

EXAMPLE 7

The following materials were weighed into a polyethyleneterephthalate vial and a non-metering valve was crimped in place:

	<u>(g)</u>
25 Betamethasone valerate	0.100
Lipoid™ S100 phosphatidylcholine	0.700
n-Butane	5.600
	<hr/>
30	6.400

The vial was subjected to ultrasonic energy for 30 seconds and then placed in a water bath at 55°C. After 15 minutes solubilization had been achieved; upon 35 cooling no precipitation was observed.

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EXAMPLES 8 AND 9

The following formulations were prepared:

	<u>mg/ml</u>	<u>(g)</u>
Drug	2.00	0.120
5 Epikuron™ 200 phosphatidylcholine	14.00	0.841
n-Butane	113.32	6.808
Drivosol™ 32*	339.96	20.423
Dimethylether	113.32	6.808
10	<hr/> 582.60	<hr/> 35.000

*A mixture containing 77 percent isobutane, 4 percent n-butane, and 19 percent propane by weight.

15 The drug (atropine in Example 8 and captopril in Example 9) and the phosphatidylcholine were weighed into a plastic coated glass bottle which was then sealed with a non-metering valve. The required quantity of n-butane was then pressure-filled into the
20 sealed bottle to form a concentrate. The sealed bottle was then heated for 1 hour at 55°C in a water bath. The sealed bottle was then allowed to cool to room temperature and the remaining propellants were filled into the bottle.

25

EXAMPLE 8

The drug, atropine (base), was solubilized within 1 hour in the concentrate and remained in solution when the remaining propellants were added.

30

EXAMPLE 9

The drug, captopril, was solubilized within one hour in the concentrate and remained in solution when the remaining propellants were added.

35

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EXAMPLES 10 AND 11

The following formulations were prepared:

	<u>mg/ml</u>	<u>(g)</u>
Drug	2.00	0.104)
5 Epikuron™ 200	14.00	0.725)
n-Butane (20%)	112.66	5.834) concen-
Ethanol (2.5%)	14.08	0.729) trate
Drivosol 32 (60%)	337.98	17.503
Dimethylether (17.5%)	98.58	5.105
10	<hr/>	<hr/>
	579.300	30.000

The formulations were prepared by weighing the drug (propranolol hydrochloride in Example 10 and
15 diazepam in Example 11), the phosphatidylcholine, and the ethanol into a glass vial, sealing the vial with a non-metering valve and pressure filling the required amount of n-butane into the sealed vial to form a concentrate. Each vial was then heated at 55°C for 2
20 hours in a water bath. The vials were allowed to cool to room temperature and the remaining propellants were filled into the vials.

The drugs both solubilized in the concentrate and remained in solution after cooling to room temperature
25 and after remaining propellants were added.

In separate tests it was not possible to achieve solubilization of the drugs in the concentrate in absence of ethanol.

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CLAIMS

1. An aerosol formulation which contains substantially no dispersed phase, comprising: an
5 aerosol propellant system comprising a propellant selected from n-butane, dimethylether and mixtures thereof; a glycerol phosphatide; and a drug, in which the drug is dissolved in the composition in an amount greater than could be achieved in the absence of the
10 glycerol phosphatide.
2. A formulation according to Claim 1, wherein the propellant system further comprises a copropellant selected from isobutane, propane, and mixtures thereof.
15
3. A formulation according to Claim 1 or Claim 2 in which the glycerol phosphatide is selected from phosphatidylcholine, phosphatidylserine, diphosphatidylglycerol, phosphatidic acid, and mixtures
20 thereof.
4. A formulation according to Claim 3 in which the glycerol phosphatide is phosphatidylcholine.
- 25 5. A formulation according to any preceding Claim in which the glycerol phosphatide is purified.
6. A formulation according to any preceding Claim in which the ratio of glycerol phosphatide to
30 propellant is 0.01 to 20 : 100.
7. A formulation according to any preceding Claim in which the ratio of glycerol phosphatide to
propellant is 0.01 to 10 : 100.

35

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8. A formulation according to any preceding Claim in which the ratio of glycerol phosphatide to propellant is 0.01 to 3 : 100.

5 9. A formulation according to any preceding Claim in which the ratio of drug to glycerol phosphatide is 1 to 500 : 100.

10 10. A formulation according to any preceding Claim in which the ratio of drug to glycerol phosphatide is 1 to 30 : 100.

15 11. A formulation according to any preceding Claim in which the ratio of drug to glycerol phosphatide is 2 to 10: 100.

20 12. A formulation according to any preceding Claim which additionally comprises a cosolvent in an amount effective to enhance solubilization of the drug.

13. A formulation according to Claim 12 in which the cosolvent is ethanol.

25 14. A formulation according to any preceding Claim in which the drug is selected from beclomethasone dipropionate, betamethasone dipropionate, acetate, valerate and base thereof, albuterol, atropine base, and prednisolone.

30 15. A formulation according to any one of Claim 1 to 13 in which the drug is selected from diazepam, lorazepam, atropine, captopril, propranolol hydrochloride, hydrocortisone, fluocinolone acetonide, triamcinolone acetonide, xylometazoline hydrochloride, 35 bitolterol mesylate, and lacticortone.

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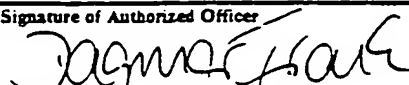
16. A formulation according to any preceding Claim containing less than 5% by weight of chlorofluorocarbons.

5 17. A formulation according to Claim 16 which is free of chlorofluorocarbons.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 92/07379

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 A61K9/00; A61K9/12		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	GB,A,2 240 271 (EUROCELTIQUE S.A.) 31 July 1991	1-4, 16, 17
Y	see claim 1 see page 2, line 28 - page 3, line 5 see page 3, line 9 - line 11 ---	5-15
X	WO,A,9 111 496 (BOEHRINGER INGELHEIM GMBH) 8 August 1991 see claims 1-6 ---	1-4
Y	WO,A,8 604 233 (RIKER LABORATORIES INC) 31 July 1986 cited in the application see the whole document ---	5-11, 14, 15
-/--		
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IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
29 OCTOBER 1992	20. 11. 92	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	 Mme Dagmar FRANK	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	GB,A,970 027 (REVLON INC.) 16 September 1964 see claims 1,3 see page 2, line 41 - line 43 see page 2, line 63 - line 71 -----	12,13

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. US 9207379
SA 64601**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
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		EP-A-	0496138	29-07-92
		JP-A-	4210918	03-08-92

WO-A-9111496	08-08-91	DE-A-	4003270	08-08-91
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		EP-A, B	0209547	28-01-87
		JP-T-	62501906	30-07-87
		US-A-	4814161	21-03-89

GB-A-970027		None		
